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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/620,642	07/16/2003	Krisztina M. Zsebo	01017/33718B	9682

4743 7590 10/17/2006

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EXAMINER	
BUNNER, BRIDGET E	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 10/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/620,642	ZSEBO ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 July 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *71-90* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *71-90* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *31 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 24 July 2006 has been entered in full. Claims 72-74, 78, and 80 are amended.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 71-90 are under consideration in the instant application.

Withdrawn Objections and/or Rejections

1. The objections to the specification at pg 2-3 of the previous Office Action (20 April 2006) are *withdrawn* in view of the amended specification (24 July 2006).

2. The rejection of claims 78 and 80 under 35 U.S.C. 112, second paragraph, as set forth at pg 8-9 of the previous Office Action (20 April 2006) is *withdrawn* in view of the amended claims (24 July 2006).

Sequence Compliance

3. The Applicant's response to the Sequence Listing Requirement under 37 CFR §1.821 (24 July 2006) has been considered and is found persuasive. Therefore, the requirement set forth in the previous Office Action (20 April 2006) is *withdrawn*.

New Claim Objections

4. Claims 73 and 74 are objected to because of the following informalities:

4a. In line 5 of claim 73, the term "SEQ ID NO 61" should recite "SEQ ID NO: 61".

4b. In line 3 of claim 74, the term "SEQ ID NO 63" should recite "SEQ ID NO: 63".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. Claims 71-90 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The basis for this rejection is set forth for claims 71-90 at pg 3-8 of the previous Office Action (20 April 2006).

Claims 71-90 are directed to a method of stimulating growth of stromal cells in a human comprising administering to the human an effective amount of a human stem cell factor (SCF) polypeptide and optionally a pharmaceutically acceptable carrier. The claims recite that the SCF polypeptide is selected from the group consisting of amino acids 1-162, 1-164, and 1-165 as set out in SEQ ID NO: 46. The claims recite that the SCF polypeptide consists of the amino acid sequence 1-130, 1-133, 1-137, 1-141, 1-145, 1-148, 1-152, 1-156, 1-157, 1-158, 1-159, 1-160, 1-161, 1-163, 1-166, 1-168, 1-173, 1-178, 2-164, 2-165, 5-164, 11-164, 1-180, 1-183, 1-185, 1-188, 1-189, 1-220, and 1-248 as set out in SEQ ID NO: 61. The claims recite that the SCF polypeptide is selected from the group consisting of amino acids 1-152, 1-157, 1-160, 1-161, and 1-220 as set out in SEQ ID NO: 63. Additionally, the claims recite that the stem cell factor is co-administered with at least one or more cytokines selected from a group consisting of IL-1, IL-2, Il-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, EPO, G-CSF, GM-CSF, CSF-1, IGF-1, and LIF. The claims recite that the pharmaceutically acceptable carrier is suitable for topical delivery, oral delivery, parenteral delivery, pulmonary delivery, and nasal delivery.

Applicant's arguments filed 24 July 2006 have been fully considered but they are not persuasive.

(i) At pg 10 of the Response of 24 July 2006, Applicant argues that the art teaches that stromal cells are capable of stimulation by SCF. Applicant indicates that Parrott et al. (Endocrinol 138: 3819-3827, 1997) teaches SCF stimulates ovarian theca cells. Applicant asserts that theca cells are considered stromal cells of the reproductive system and that they are important in development of the female reproductive tract, which the specification teaches is one of several non-hematopoietic activities in which SCF plays a role.

Applicant's arguments have been fully considered but are not found to be persuasive. The experiments performed by Parrott et al. are not commensurate in scope with the instant claims. Specifically, Parrot et al. disclose that SCF stimulates theca cell growth and androstenedione production (abstract; pg 3824). However, Parrott et al. does not teach that SCF stimulates the growth (i.e., proliferation) of stromal cells *in vitro* or *in vivo*, as required by the instant claims.

Applicant asserts that theca cells are considered stromal cells of the reproductive system. However, it must be emphasized that arguments of counsel alone cannot take the place of evidence in the record once an examiner has advanced a reasonable basis for questioning the disclosure. See *In re Budnick*, 537 F.2d at 538, 190 USPQ at 424; *In re Schulze*, 346 F.2d 600, 145 USPQ 716 (CCPA 1965); *In re Cole*, 326 F.2d 769, 140 USPQ 230 (CCPA 1964). For example, in a case where the record consisted substantially of arguments and opinions of applicant's attorney, the court indicated that factual affidavits could have provided important evidence on the issue of enablement. See *In re Knowlton*, 500 F.2d at 572, 183 USPQ at 37; *In re Wiseman*, 596 F.2d 1019, 201 USPQ 658 (CCPA 1979). The state of the art is such that theca cells are endocrine cells located exclusively in the ovary (Magoffin, DA, Int J Biochem Cell Biol 37: 1344-1349, 2005; pg 1344, 1st paragraph). Magoffin also teaches that although the theca

cells are located in the interfollicular stroma, they are closely associated with the basal lamina of ovarian follicles and can be considered an important element of the developing ovarian follicle (pg 1344, col 1-2). Parrot et al. also state that "[t]heca-granulosa cell interactions are an example of an important mesenchymal-epithelial cell interaction in the ovary" (pg 3824, col 1, first full paragraph). Thus, the state of the art is such that theca cells are not considered to be stromal cells, as asserted by Applicant.

Furthermore, the specification of the instant application broadly teaches that "[e]nhancement of growth in non-hematopoietic *stem cells* [emphasis added] such as primordial germ cells, neural crest derived melanocytes, commissural axons originating from the dorsal spinal cord, crypt cells of the gut, mesonephric and metanephric kidney tubules, and olfactory bulbs is of benefit..." (pg 28, lines 3-8). The specification also continues to disclose that SCF may be useful during *in vitro* fertilization procedures, in treatment of infertility states, or to treat intestinal damage resulting from irradiation or chemotherapy (pg 28, lines 11-14). However, the specification does not specifically teach that SCF stimulates *theca cells or stromal cells*. Furthermore, the specification does not teach any methods or working examples that stimulate the growth of stromal cells *in vitro* or in any subject by administration of SCF alone or in combination with a cytokine. Even if the instant specification or the art had incubated stromal cells in culture with SCF and demonstrated cell growth, Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, pg. 4) teaches that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of

histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (pg 4, see Major Differences *In vitro*). Clearly, it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment.

In addition, regarding *in vivo* administration, variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy. Although the instant specification discloses that there are no adverse reactions to the administration of SCF, one skilled in the art would not be able to predict the effects of SCF in the stimulation of stromal cell growth. The peptide may not otherwise reach the target cell because of its inability to penetrate tissues or cells where its activity is to be exerted, it may be absorbed by fluids, cells and tissues where it has no effect, circulation into the target area may be insufficient to carry the peptide, and a large enough local concentration may not be established (see Pettit et al., cited previously by Examiner). The specification provides insufficient guidance with regard to these issues and provides no working examples or evidence which would provide guidance to one skilled in the art to predict the efficacy of the claimed methods with a reasonable expectation of success. Thus, undue experimentation would be required of one skilled in the art at the time the invention was made to determine the efficacy of growth of stromal cells in a subject by administration of SCF or a SCF-cytokine composition.

(ii) Applicant argues that Krieger et al. (Eur J Haematol 54: 262-269, 1995) disclosed that stromal cells isolated from patients with aplastic anemia expressed only low levels of soluble SCF, and that addition of exogenous SCF to the cell culture resulted in growth of the bone marrow stromal cells.

Applicant's arguments have been fully considered but are not found to be persuasive. The post-filing date reference, Krieger et al., disclose that SCF *alone* added to stroma cell cultures was not effective in stroma growth (pg 267, col 1; Figure 5). Krieger et al. indicate that SCF was essential in combination with other growth factors for stroma growth (pg 267, col 1; Figure 5). However, Krieger et al. and the instant specification do not teach any methods or working examples that stimulate the growth of stromal cells in any subject, particularly a human, by administration of SCF alone or in combination with a cytokine.

(iii) Applicant also argues that Simak et al. (Histol Histopathol 15: 365-374, 2000) teach that both SCF and c-kit transcripts were present in cultured epithelial cells of benign hyperplasia (BPH) isolates, and in cultures of stroma cells from both normal and BPH. Applicant contends that these references indicate that a worker of ordinary skill can readily isolate stromal cells from stem cells or other cells in culture, and readily assess the effects of SCF on this stromal cell population.

Applicant's arguments have been fully considered but are not found to be persuasive. The Examiner acknowledges that a skilled artisan may be able to isolate and culture stromal cells. However, as discussed in the previous Office Action, the state of the art is such that stromal cells *produce* stem cell factor (see pg 177, lines 14-15; Huang et al., Cell 63: 225, 1990;

Zsebo et al., Cell 63: 213, 1990; Williams et al., Cell 63: 167, 1990). The specification of the instant application and relevant literature do not teach any methods or working examples that stimulate the growth of stromal cells in any subject, particularly a human, by administration of SCF alone or in combination with a cytokine. This is not adequate guidance, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Additionally, as was found in Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987), a single embodiment may provide broad enablement in cases involving predictable factors such as mechanical or electrical elements, but more will be required in cases that involve unpredictable factors such as most chemical reactions and physiological activity. See also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991). The present invention is unpredictable and complex wherein one skilled in the art may not necessarily stimulate the growth of stromal cells in a human with SCF. Krieger et al. even state that the apparent deficiency of SCF in aplastic anemia may be overcome *in vivo* by redundant activities of other hematopoietic growth factors and be of no functional consequence (pg 268, col 2).

(iv) Applicant submits that a worker of ordinary skill in the art would reasonably expect that the amounts of SCF used to stimulate bone marrow growth as taught in the specification would be similar to amounts necessary to stimulate growth of stromal cells. Applicant indicates that the SCF concentrations used in Parrott et al. are similar to the effective amount of SCF disclosed in the specification to stimulate bone marrow cells. Applicant concludes that both the teachings in

the specification and the art show the SCF polypeptide bind to and stimulate its receptor on a multiplicity of cell types, including stromal cells, within relatively the same concentration ranges. Applicant argues that the specification teaches that the administration of SCF presents no adverse reactions and thus, the administration of SCF is predictable. Applicant contends that any SCF polypeptide analog or isoform binds to the SCF receptor on the cell surface and activates the receptor. Applicant cites Lev et al. (J Biol Chem 267 : 10866-10873, 1992), which teaches that CHO cells transfected with SCF receptor were bound and activated by SCF. Applicant states that a worker of ordinary skill in the art would reasonably expect that the same SCF polypeptide would bind to the same SCF receptor on a stromal cell, thereby stimulating said stromal cells.

Applicant's arguments have been fully considered but are not found to be persuasive. While the SCF concentrations utilized in Parrot et al. may overlap with the concentrations disclosed in the instant specification, neither Parrott et al. nor the instant specification stimulate the growth of stromal cells in a human by administering SCF. The specification of the instant application only monitors red blood cell, platelet, and white blood cell numbers after administration of SCF. The specification does not monitor stromal cell populations or even disclose that the SCF receptor is present on stromal cells. Furthermore, as discussed in the previous Office Action, the skilled artisan would not be able to predict the effects of administration of a SCF polypeptide or SCF-cytokine composition since it cannot be determined from the specification of the instant application or the claims which stromal cells are being targeted for the stimulation of growth. Stromal cells are present for example, in the bone marrow, thymus, and endometrium (see for instance, Derubeis et al. Ann Biomed Engineer

32(1): 160-164, 2004; Anderson et al. Annu Rev Immunol 14: 73-99, 1996; Irwin et al. Endocrinol 129(5) : 2385-2392, 1991). Post-filing date references also disclose that stromal cells in these environments are heterogeneous cell populations, with different growth rates, morphologies, and markers (Bianco et al., Stem Cells 19: 180-192, 2001, pg 181; Screpanti et al., J Cell Sci 105: 601-606, 1993, pg 603-604). Therefore, undue experimentation would be required of one skilled in the art to determine the efficacy of growth of stromal cells in a subject by administration of a SCF or a SCF-cytokine composition. It is noted that the courts have stated that patent protection is granted in return for an enabling disclosure, not for vague intimations of general ideas that may or may not be patentable. Tossing out the mere germ of an idea does not constitute an enabling disclosure. Reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. See *Genentech v. Novo Nordisk A/S* (CAFC) 42 USPQ2d 1001 (1997).

Proper analysis of the Wands factors was provided in the previous Office Action. Due to the large quantity of experimentation necessary to stimulate growth of stromal cells *in vivo* and to determine the efficacy of treatment, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to same, the complex nature of the invention, and the breadth of the claims which fail to recite any specific location of the targeted stromal cells (i.e., bone marrow, thymus, endometrium, etc.) for growth stimulation, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Conclusion

No claims are allowable.

Applicant's amendment necessitated the new ground(s) of objection/rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (571) 272-0881. The examiner can normally be reached on 8:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BEB
Art Unit 1647
10 October 2006

Bridget E. Bunner

BRIDGET BUNNER
PATENT EXAMINER